Rehna Khan
Consultant Ophthalmologist

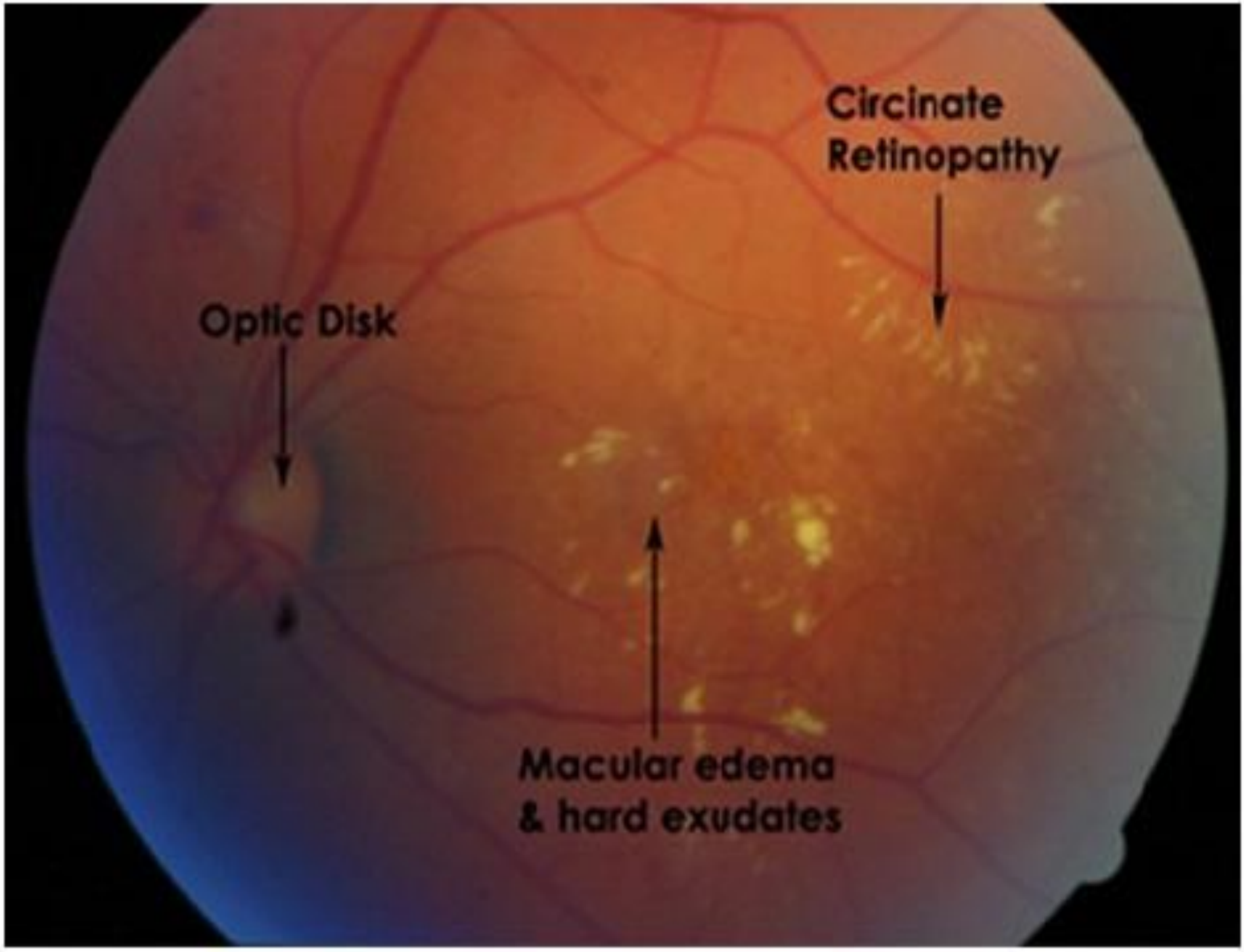
Diabetic Macular Oedema

british association of retinal screening
bars

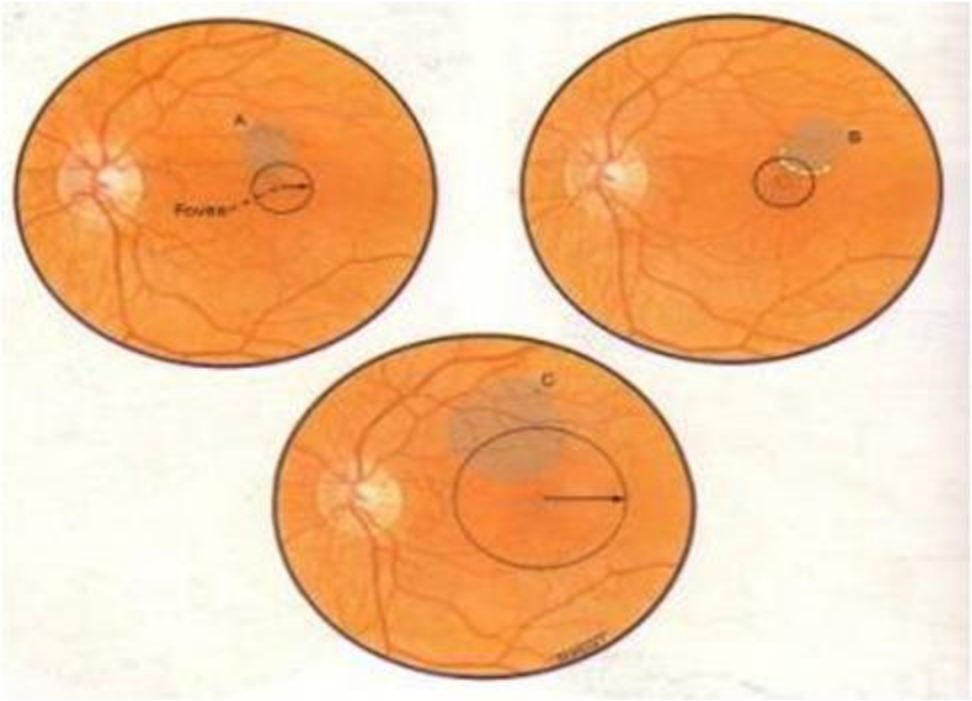
Calderdale and Huddersfield NHS
NHS Foundation Trust

Objectives

- Define terminology used in DMO
- Explain how DMO occurs
- List the treatments available today for DMO
- Explain their mode of action
- Brief overview of the evidence
- Clinical cases: patient journey from screening to treatment

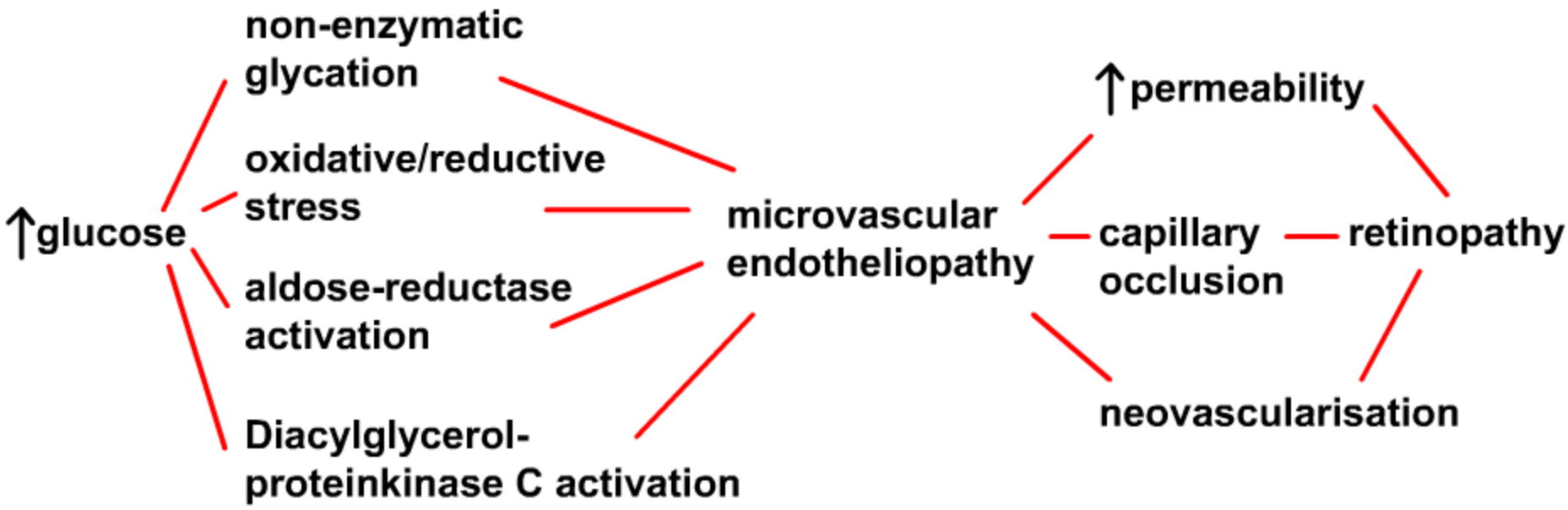

Circinate
Retinopathy
Optic Disk
Macular edema
& hard exudates

CSMO

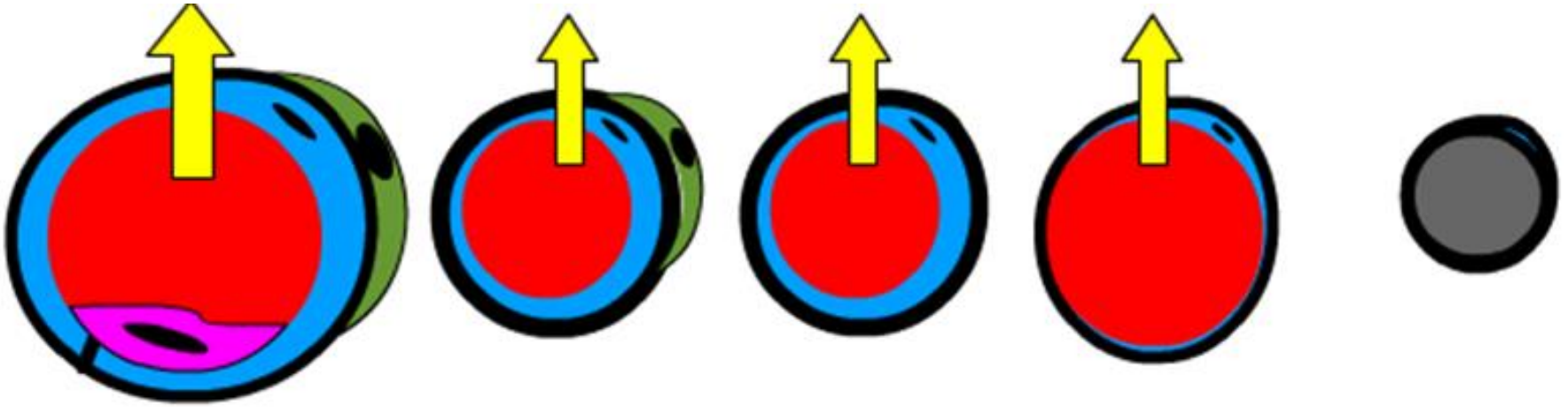


Effect of hyperglycaemia

Pathogenesis of diabetic retinopathy parts after Forrester, presented in Udine 2002, animation by D Kinshuck



Pathophysiology of DMO



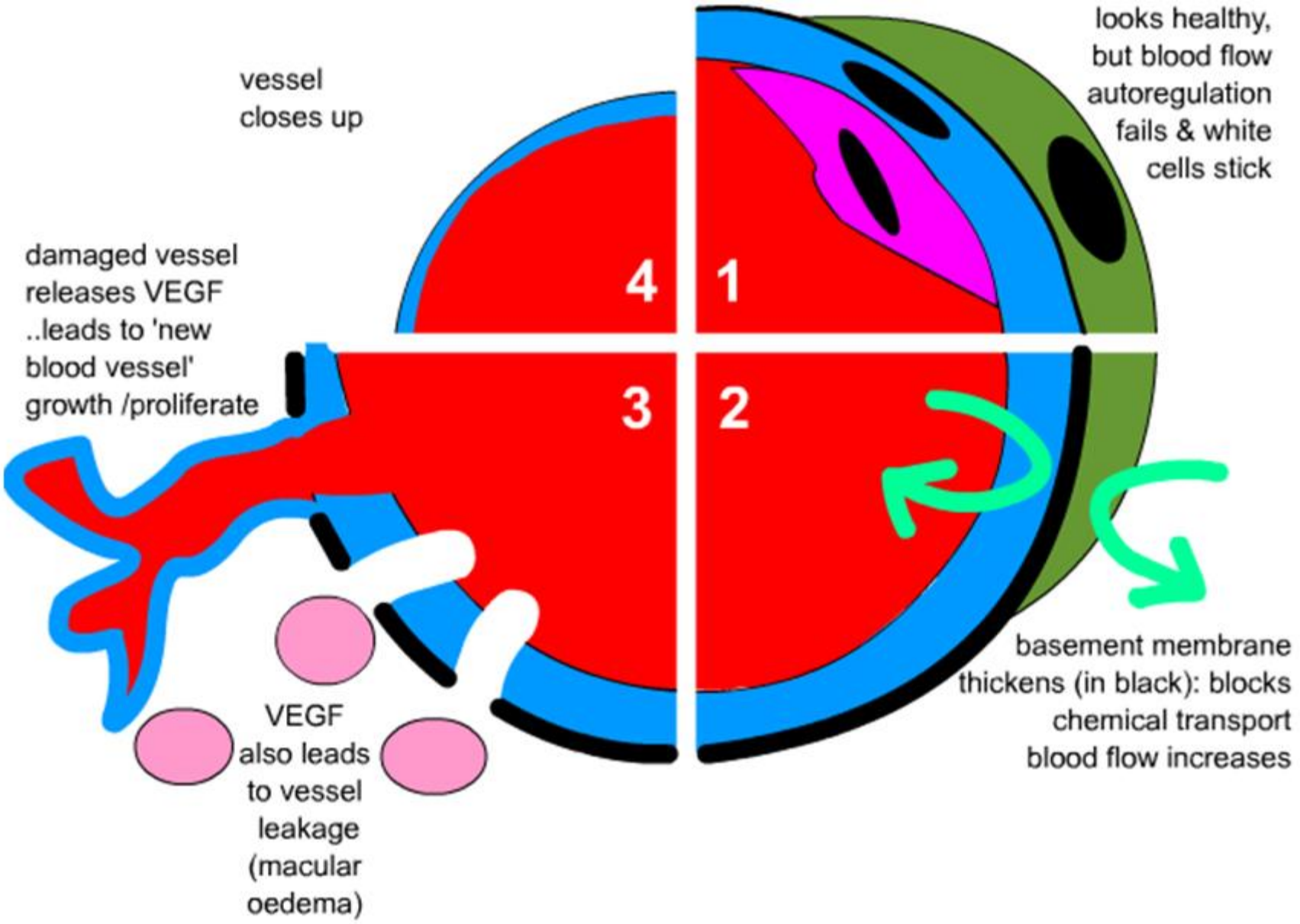
normal blood flow; white cells stick to wall

reduced blood flow; thickened basement membrane

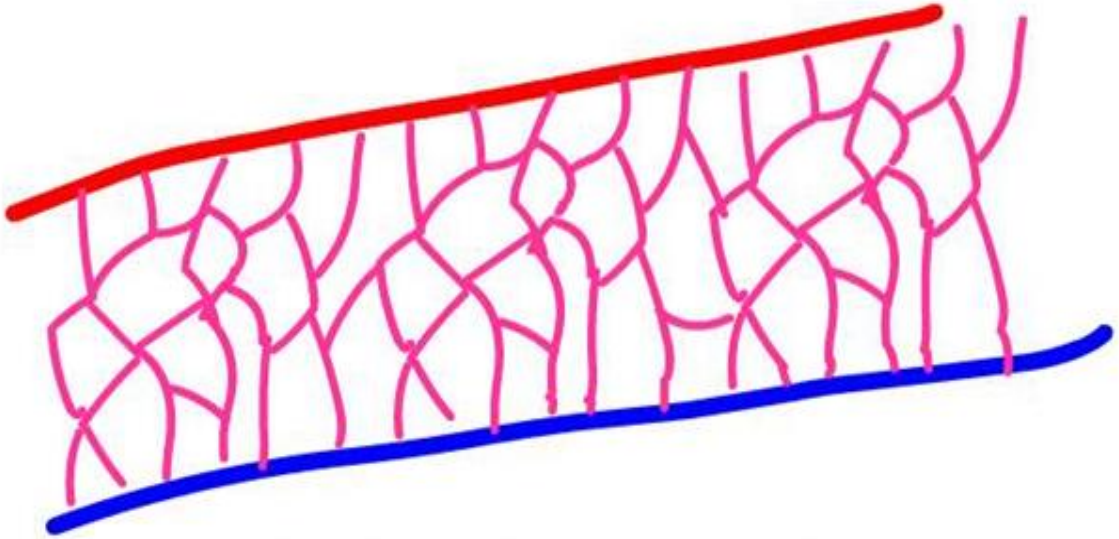
pericyte death

endothelial cell death: increased blood flow

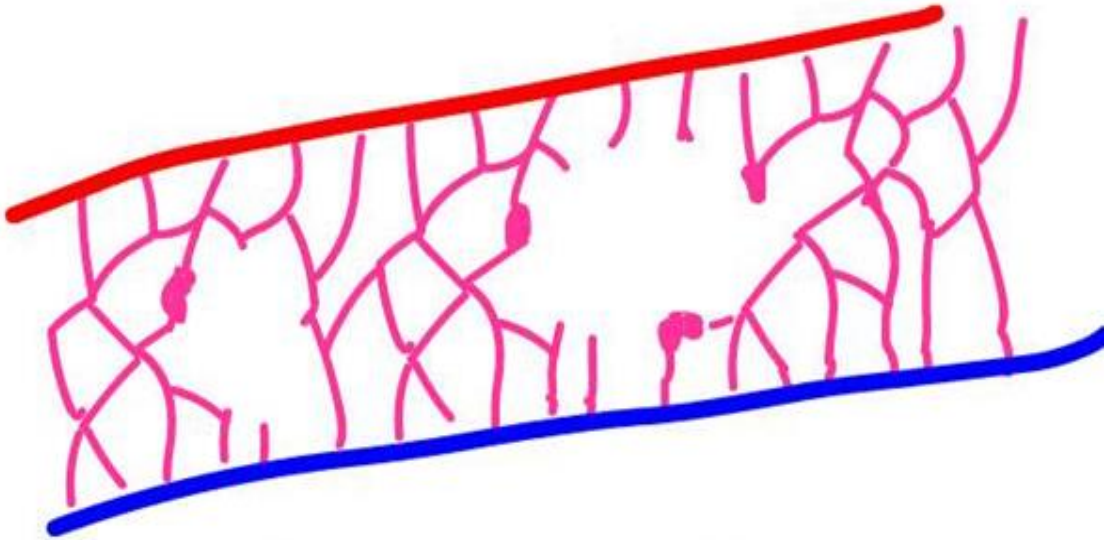
capillary closure


looks healthy, but blood flow autoregulation fails & white cells stick
vessel closes up
damaged vessel releases VEGF ..leads to 'new blood vessel' growth /proliferate
4
1
3
2
basement membrane thickens (in black): blocks chemical transport blood flow increases
VEGF also leads to vessel leakage (macular oedema)

MA

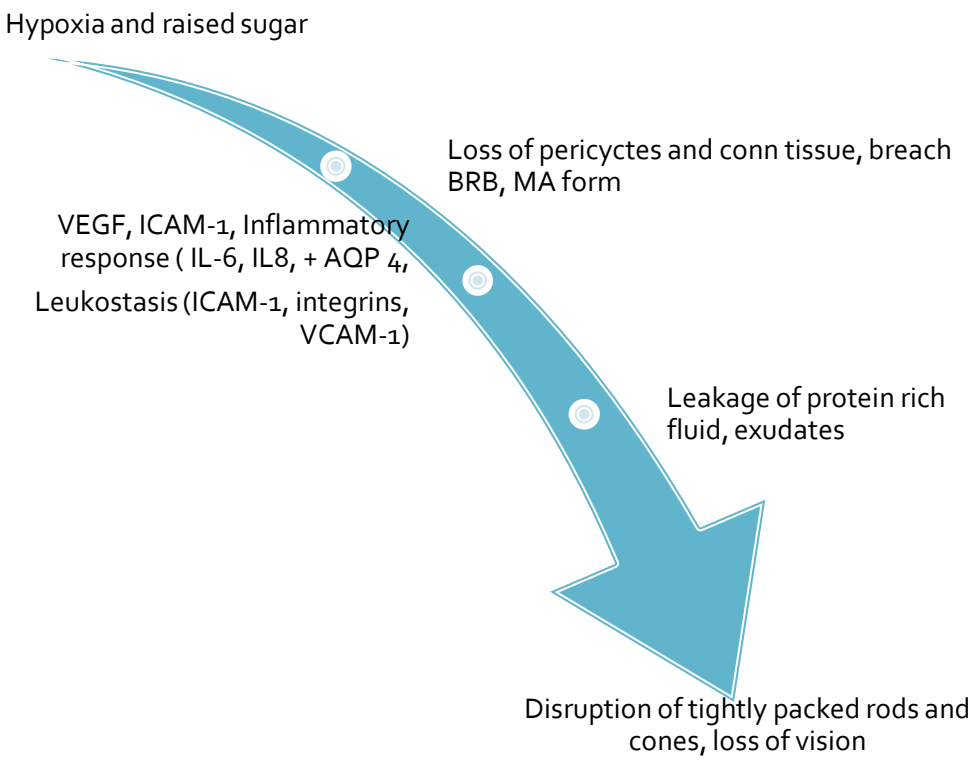


healthy retinal capillaries

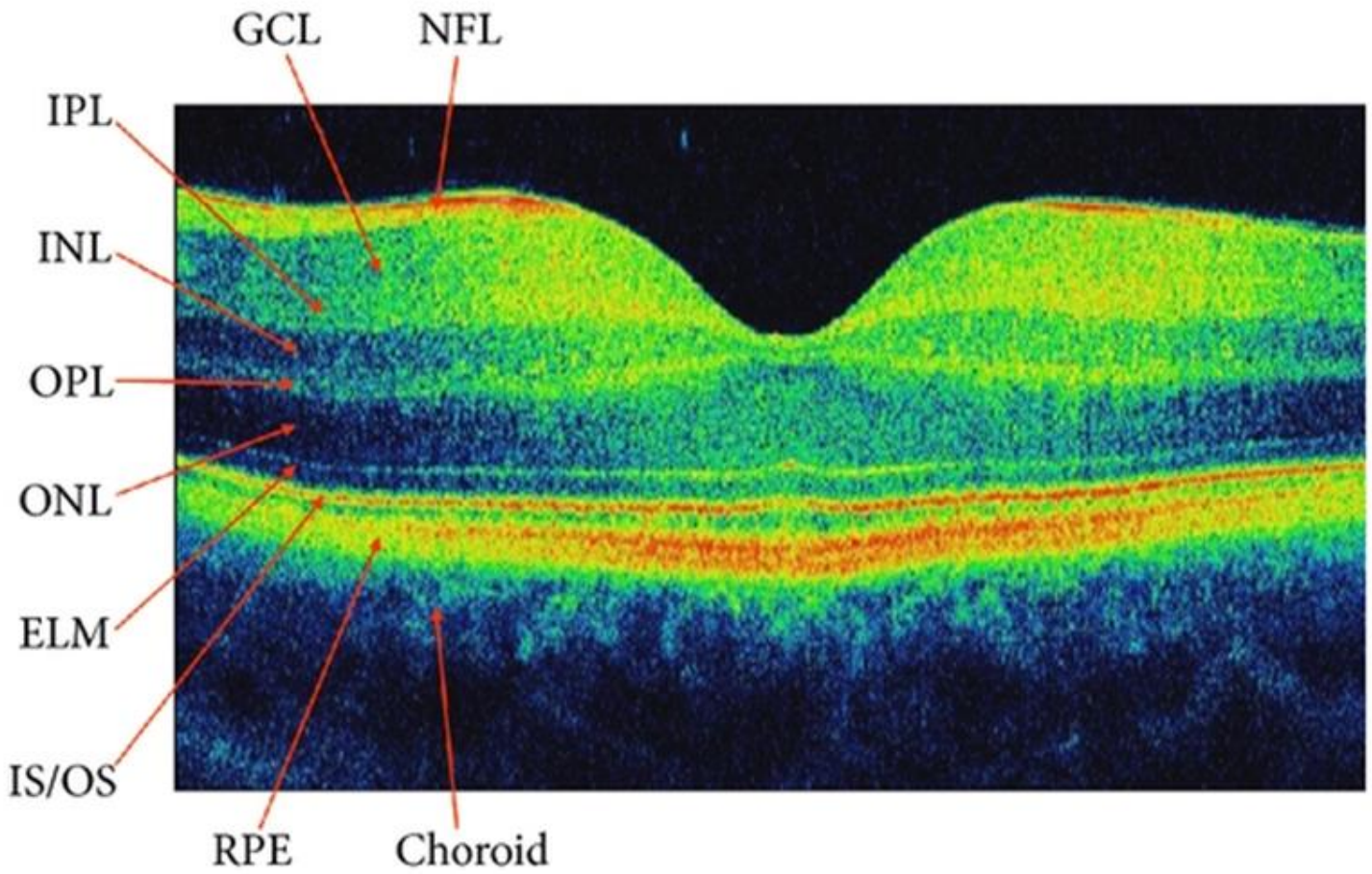


diabetic retinal capillaries:
some are closed off, others form
dilated segments 'microaneurysms'

Pathogenesis of DMO

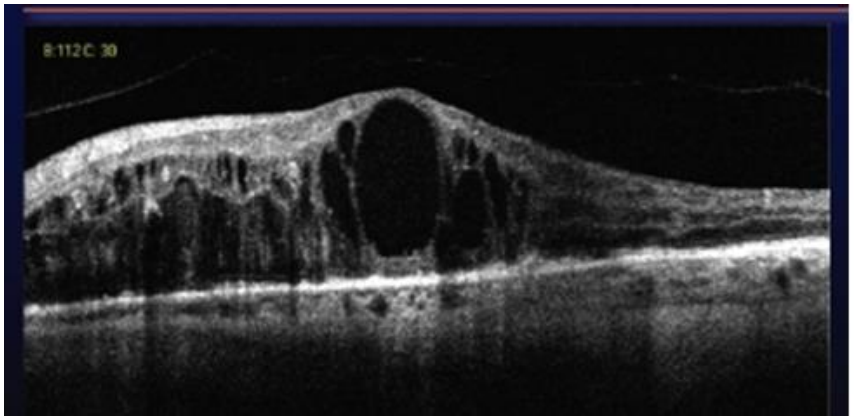


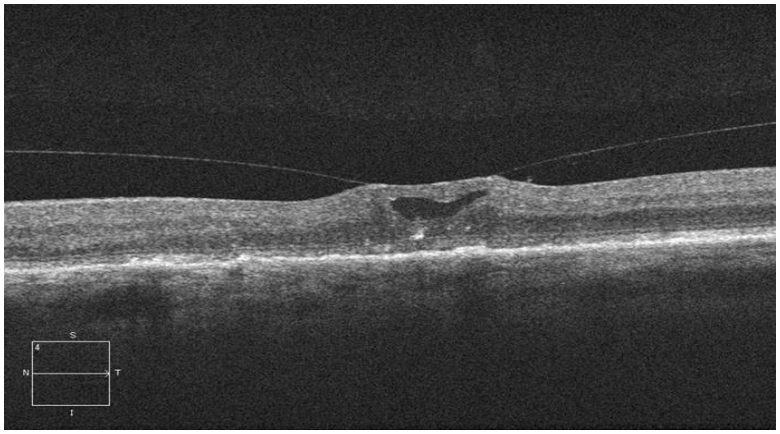
Review of normal anatomy



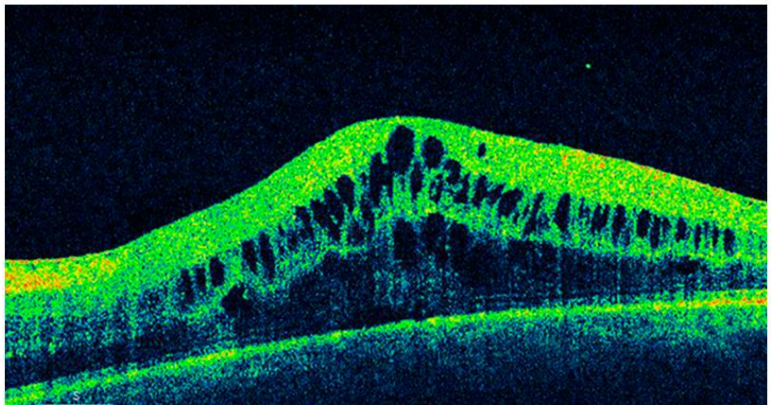
OCT diagnosis of type of DMO

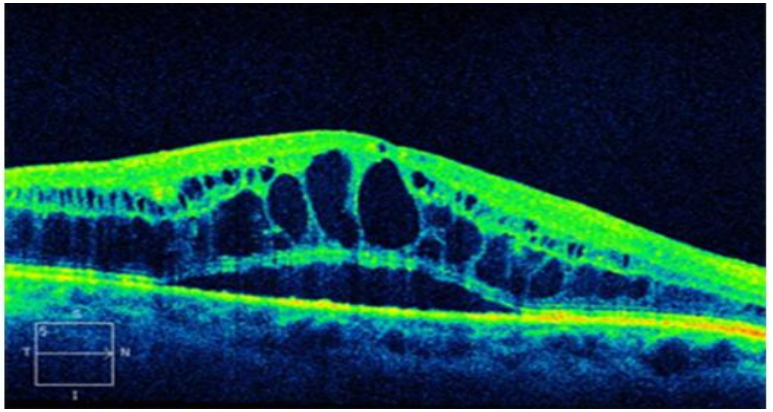
CYSTOID

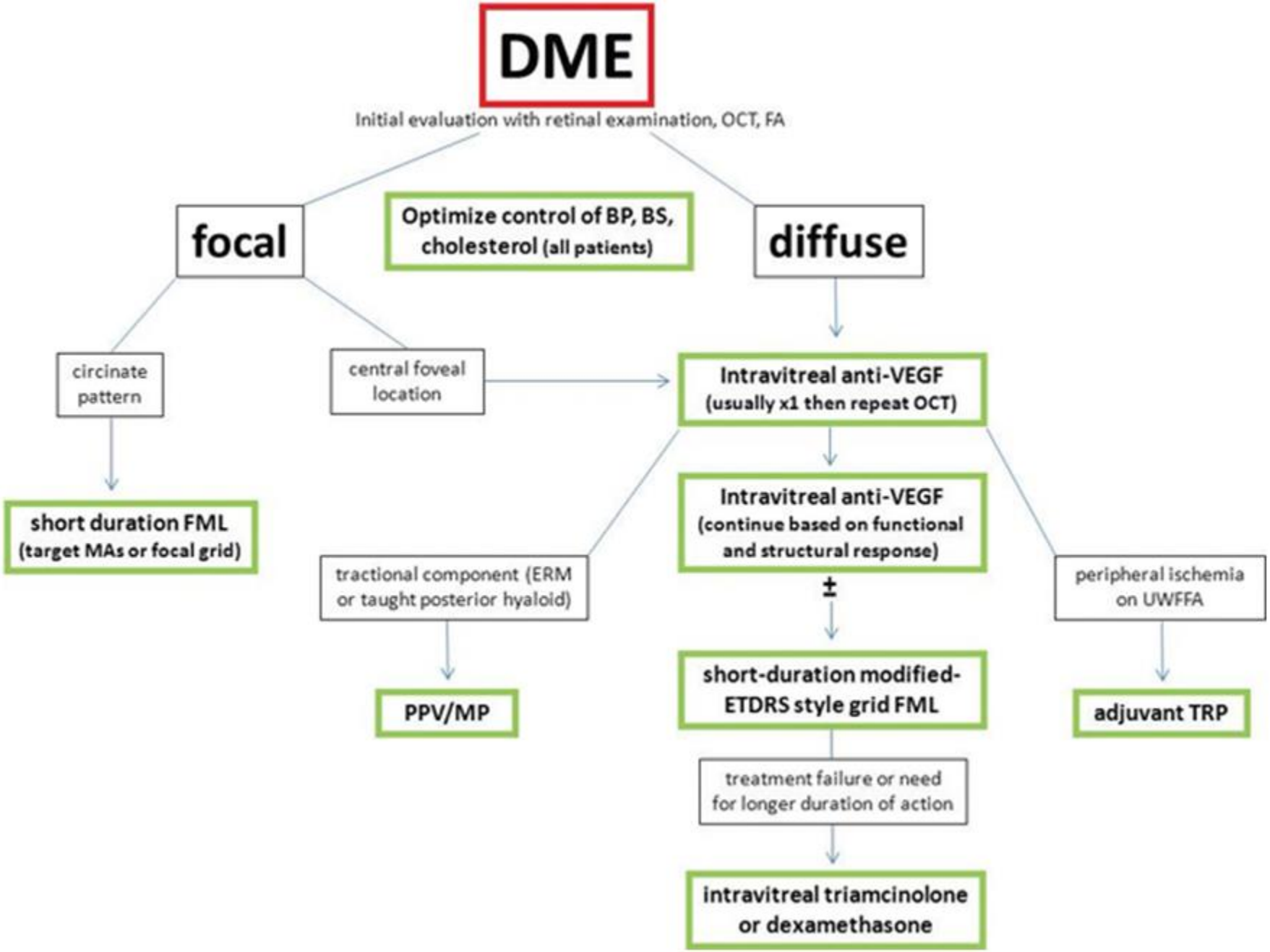




SPONGE-LIKE & COMBINED






DME
Initial evaluation with retinal examination, OCT, FA
focal
Optimize control of BP, BS, cholesterol (all patients)
diffuse
circinate pattern
central foveal location
Intravitreal anti-VEGF (usually x1 then repeat OCT)
short duration FML (target MAs or focal grid)
tractional component (ERM or taught posterior hyaloid)
Intravitreal anti-VEGF (continue based on functional and structural response)
peripheral ischemia on UWFFA
±
PPV/MP
short-duration modified-ETDRS style grid FML
adjuvant TRP
treatment failure or need for longer duration of action
intravitreal triamcinolone or dexamethasone

Macular Laser Therapy

- Macular laser treatment **was** the standard of care for sight threatening DMO
- Its efficacy was evidenced by the ETDRS (Early Treatment of Diabetic Retinopathy) study.
- A reduction in the risk of losing 2 lines on the Snellen chart by 50% in a 5 year period if laser was applied where signs of clinically significant macular oedema (CSMO) were seen (Ciulla TA, 2003).
- Often a single treatment is not sufficient and laser does not reverse the visual loss experienced. At best it stabilises vision.
- The importance of systemic control cannot be emphasised enough for delaying progression and enhancing the prognosis with all therapies for DMO.

Macular Ischaemia

- If the FAZ enlarges, vision is reduced
- If vision is reduced and there is no oedema clinically, this is the likely cause: confirm on fluorescein angiogram (FFA).
- Laser is not helpful. Laser is for macular oedema, seen with OCT or clinically with a slit lamp, or FFA. Avastin is less effective if the FAZ enlarges ('ischaemic maculopathy'). The ischaemia leads to foveal atrophy.
- Fundus autofluoresence & Angio OCT are helpful in determining the degree of foveal damage

Ranibuzumab for DMO

- The RISE & RIDE study (Nguyen, 2012).

- 15 letter gain for 0.3 mg: 44.8% and 33.6%
- 15 letter gain for 0.5mg: 39.2% and 45.7%

- This was the first time a therapy resulted in an increase in vision for DMO patients.

Bevacizumab in DMO

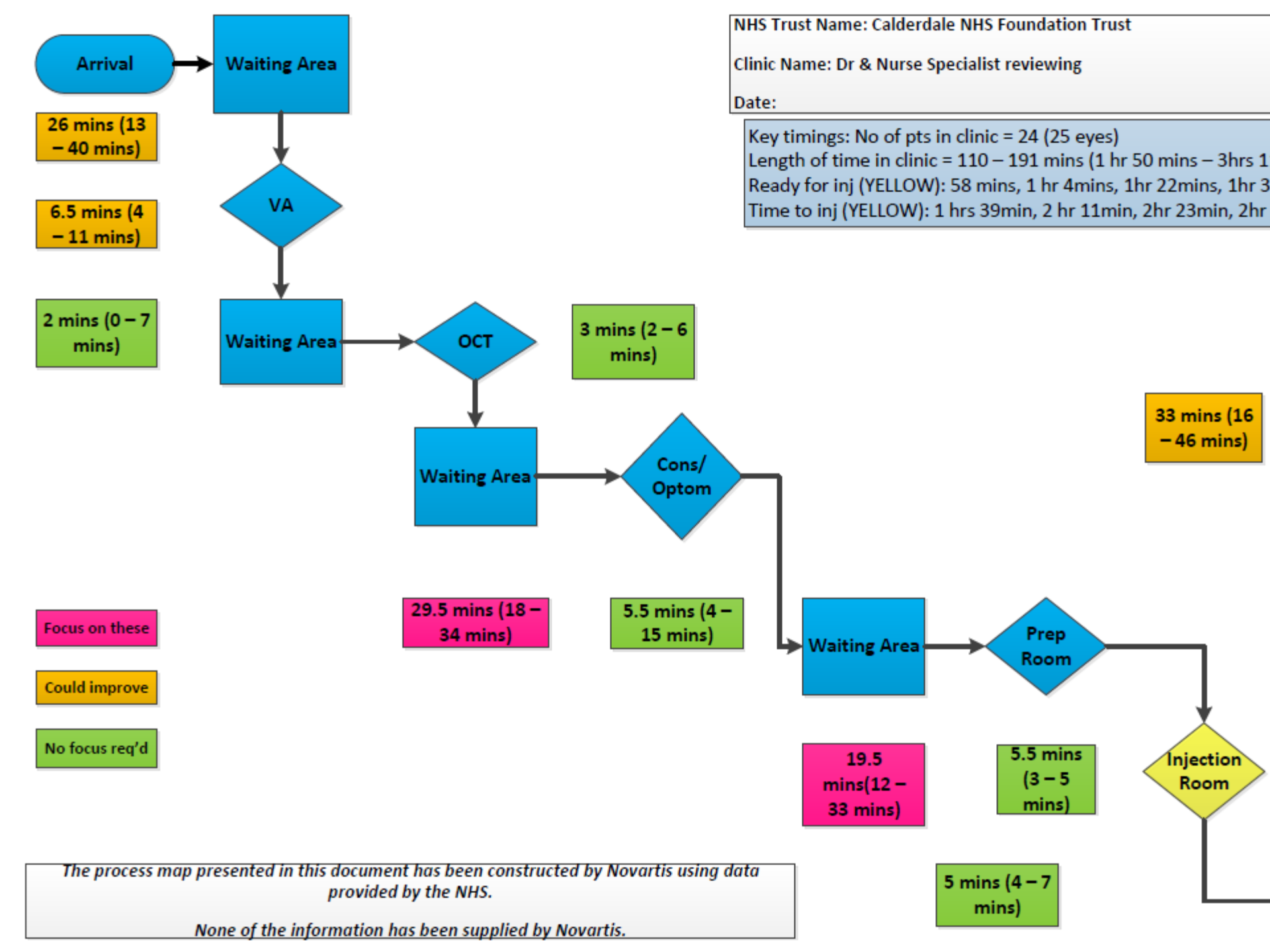
- Must be prepared in a pharmacy setting that can ensure safe supply. (Moorfields and Liverpool & Aintree).
- Legal implications using a non-licensed therapy when a licensed alternative exists
- Significant cost difference between Bevacizumab and Ranibizumab and the continuous need to find cost saving opportunities Bevacizumab is currently counted but surrounded in issues that have yet to be resolved at a policy maker or government level.

- The BOLT study
- Bevacizumab injections vs macular laser
- gain of +8 vs +0.5 letters at 12
- The median number of injections was 9 and laser treatment were 3 (Michaelides M, 2010).

Aflibercept (Eylea) VIVID and VISTA

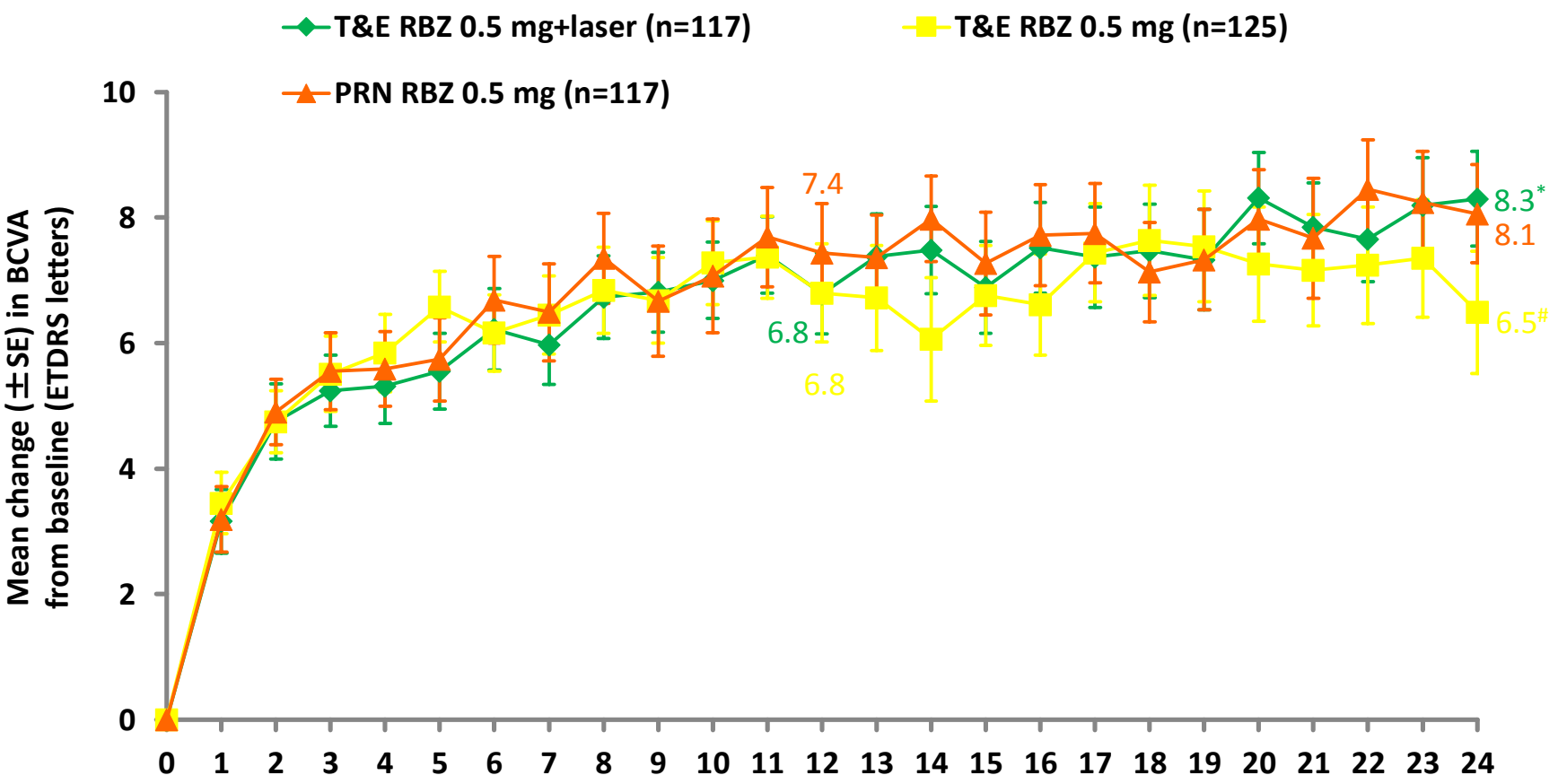
- RCT, multicentre double masked, three groups,
- 2mg Aflibercept every 4 weeks and sham laser,
- 2mg Aflibercept every 8 weeks after 5 initial monthly doses plus sham laser
- laser plus sham injections (U, 2013).

	VIVID	VISTA
4 week	+10.5	+12.5
8 week	+10.7	+10.7
Laser +sham	+1.2	+0.2


NHS Trust Name: Calderdale NHS Foundation Trust
Clinic Name: Dr & Nurse Specialist reviewing
Date:
Key timings: No of pts in clinic = 24 (25 eyes)
Length of time in clinic = 110 – 191 mins (1 hr 50 mins – 3hrs 1
Ready for inj (YELLOW): 58 mins, 1 hr 4mins, 1hr 22mins, 1hr 3
Time to inj (YELLOW): 1 hrs 39min, 2 hr 11min, 2hr 23min, 2hr
Arrival
Waiting Area
26 mins (13 – 40 mins)
VA
6.5 mins (4 – 11 mins)
2 mins (0 – 7 mins)
Waiting Area
OCT
3 mins (2 – 6 mins)
Waiting Area
Cons/ Optom
33 mins (16 – 46 mins)
29.5 mins (18 – 34 mins)
5.5 mins (4 – 15 mins)
Waiting Area
Prep Room
Injection Room
19.5 mins(12 – 33 mins)
5.5 mins (3 – 5 mins)
5 mins (4 – 7 mins)
Focus on these
Could improve
No focus req'd
The process map presented in this document has been constructed by Novartis using data provided by the NHS.
None of the information has been supplied by Novartis.

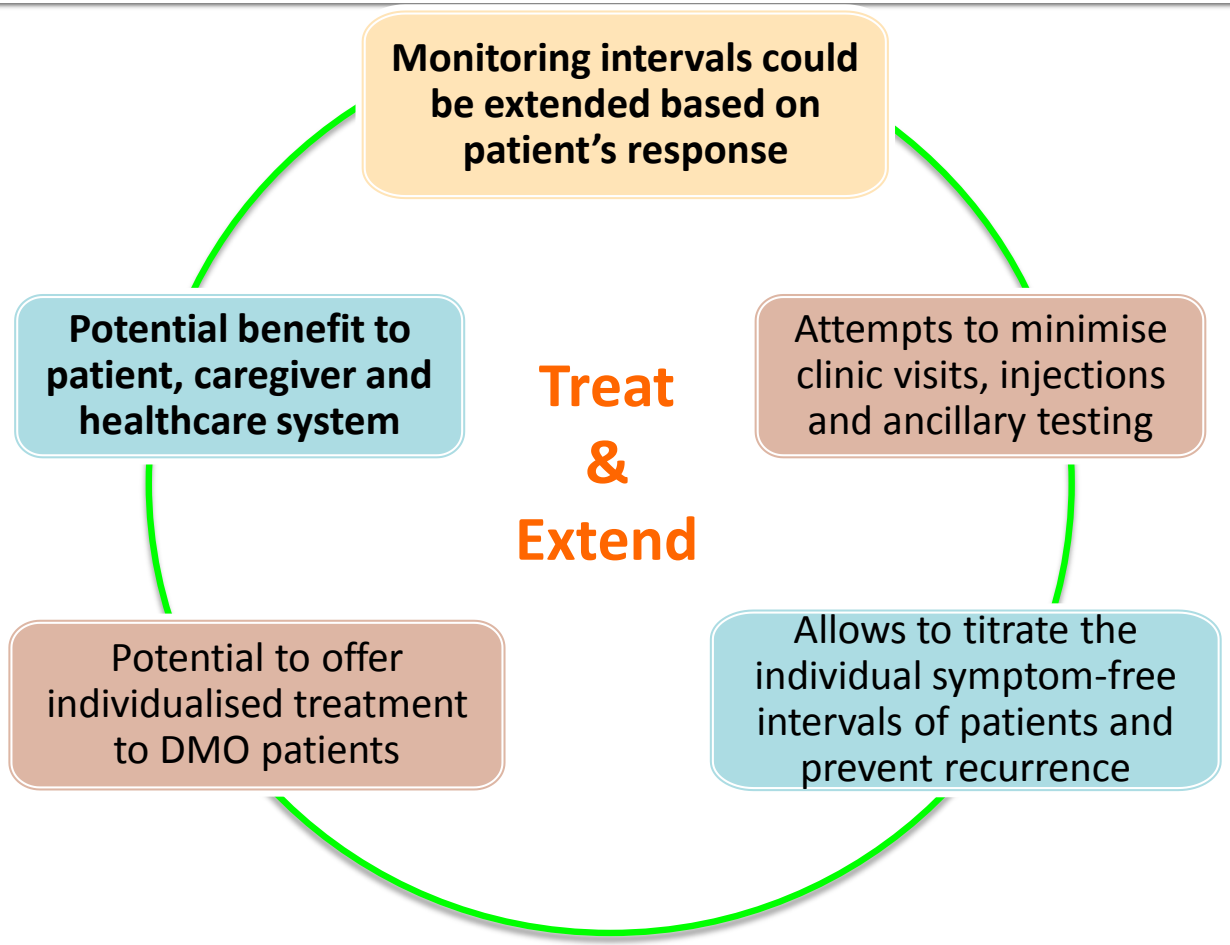
Mean change in BCVA from baseline to Month 24 was similar across the three treatment groups

No significant difference observed across treatment groups at Months 12 and 24



*p=0.9327 vs PRN; #p=0.1599 vs PRN; CMH test (row mean scores statistic) with the observed values as scores;
Full analysis set (MV/LOCF, mean value interpolation/last observation carried forward); consisted of all randomised patients who received at least one application of study treatment (ranibizumab or laser), and had at least one post baseline efficacy assessment in the study eye; Stratified analysis includes baseline visual acuity (<=60 letters, >60 letters and <=73 letters, >73 letters) as factor

Why use a Treat and Extend regimen in DMO?

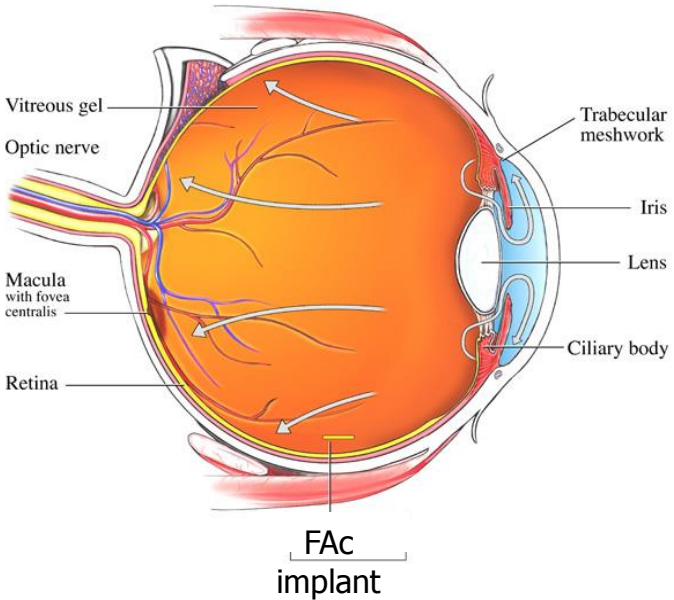


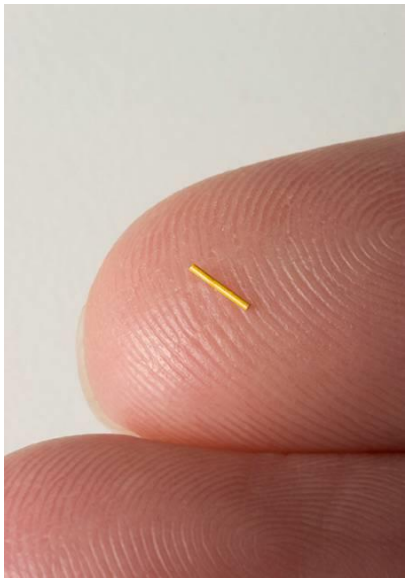
Aqueous Humour Cytokine Levels According to Severity of DR

ETDRS retinopathy severity	N	Cytokine concentration (pg/mL)					
		VEGF	IL-1β	IL-6	IL-8	MCP-1	IP-10
10	28	967.0	10.0	32.1	22.8	252.2	2.1
20	23	952.8	11.0	33.5	20.6	303.6	2.5
35	26	956.4	9.2	33.1	22.7	339.5	5.6
43	18	1084.7	10.7	33.2	24.4	468.8	5.5
47	13	1172.6	18.8	56.6	29.2	645.2	9.5
53	8	1177.3	22.7	106.7	49.4	921.2	22.3
65	7	1142.7	23.7	116.8	51.0	1215.1	31.3
75	8	1051.4	27.6	147.0	75.7	1286.6	34.3
81	5	1165.4	45.8	188.6	74.4	1630.8	29.2
P-value		.733	.003	<.001	.001	<.001	<.001

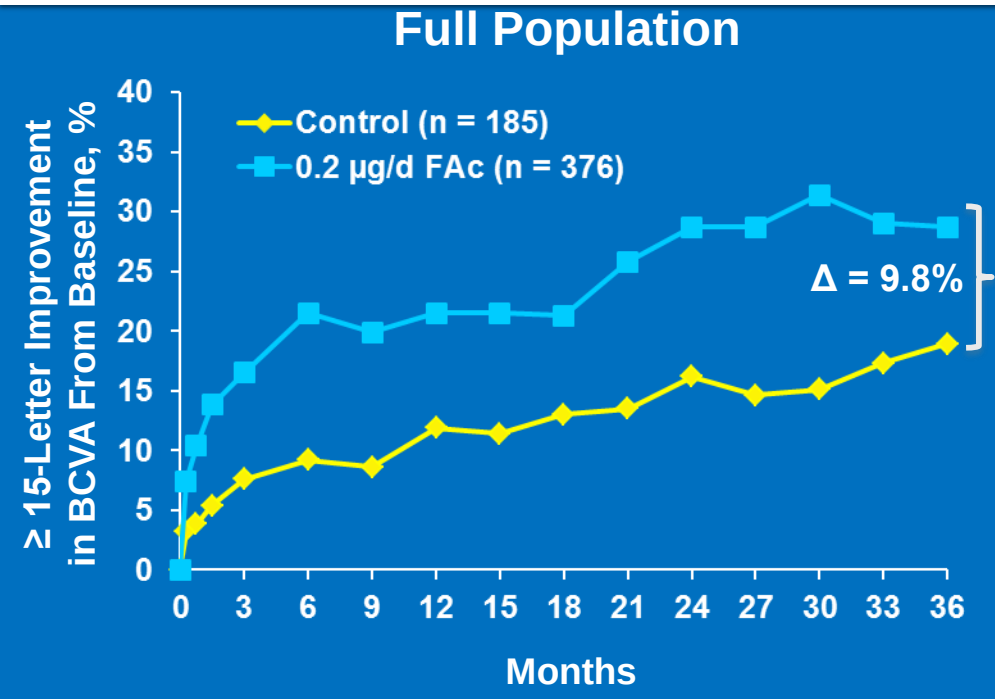
ILUVIEN Implant Technology

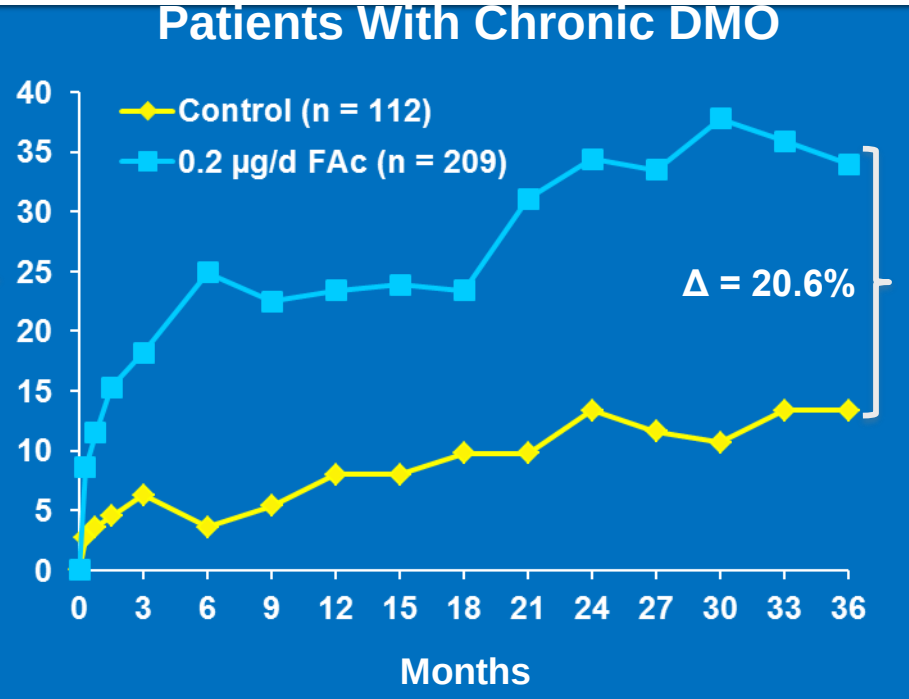
- Nonbioerodible micro implant (polyimide) containing 190µg of fluocinolone acetonide (FAc)
- Consistent daily submicrogram delivery of 0.2 µg/d FAc for up to 36 months.
- Posterior point of release
- 3.5 mm × 0.37 mm non-bioerodable micro implant.
- 25-gauge injector creates self-sealing wound.
- No measurable systemic exposure.



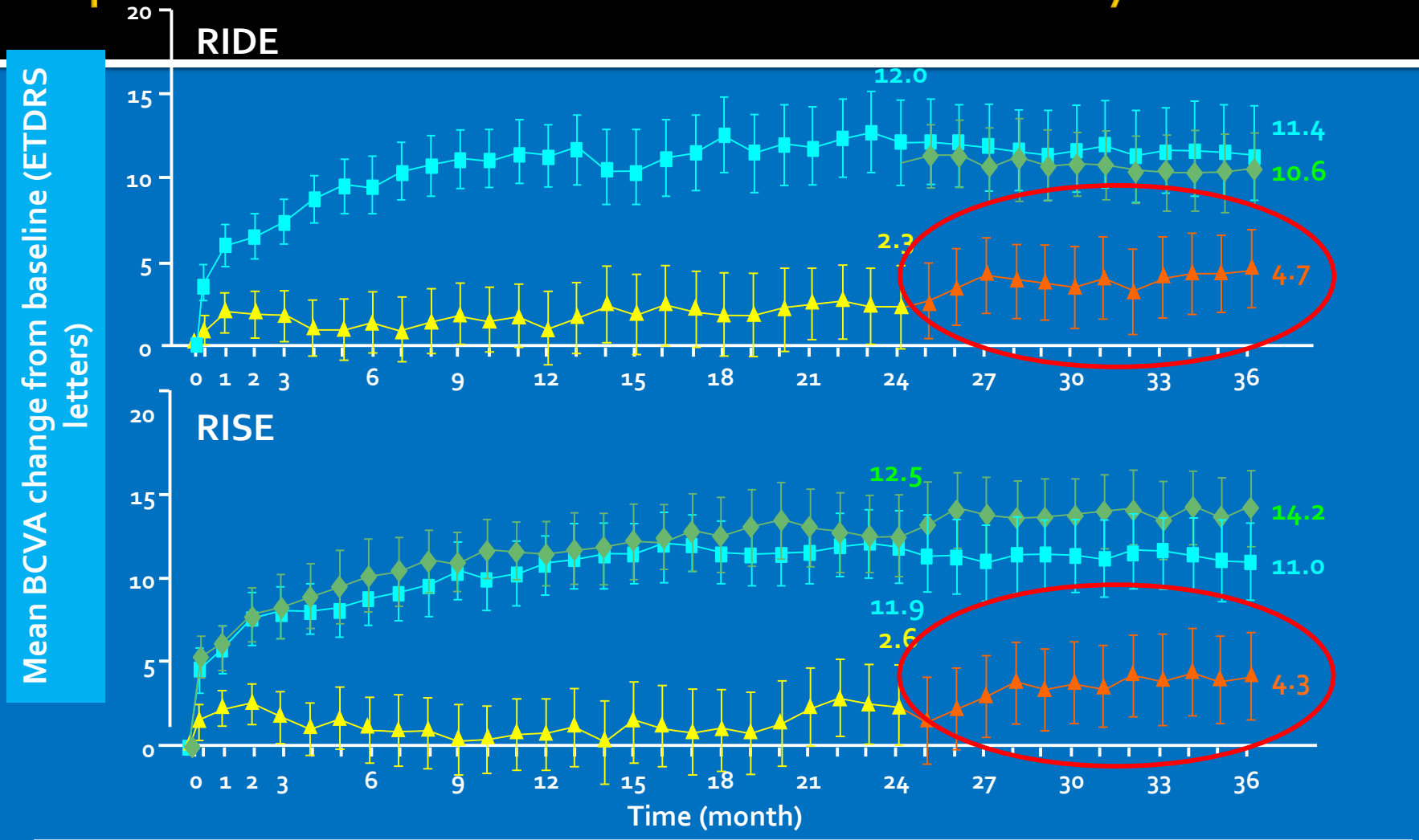


≥15 letter Gain is Greater in Chronic DMO Patients

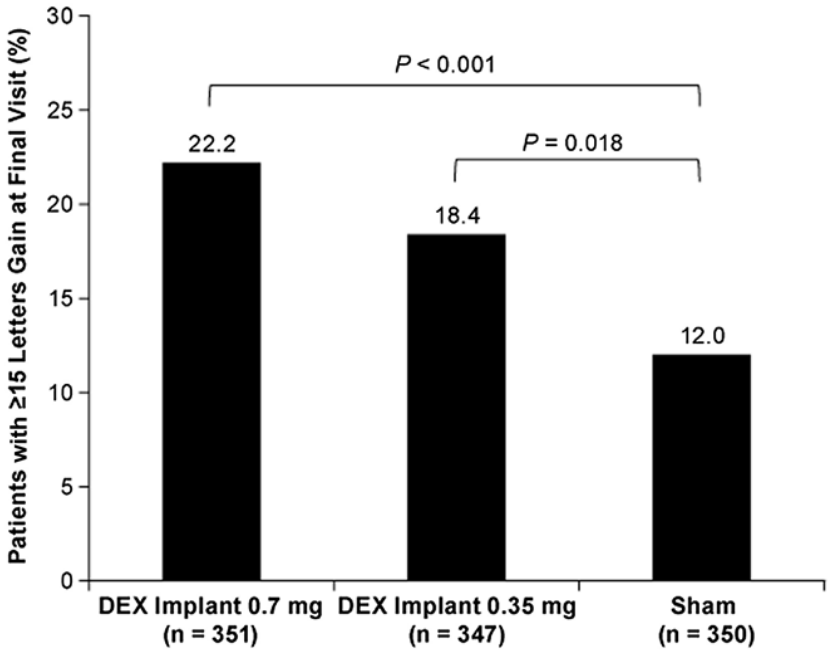




Patients Receiving Ranibizumab Late in Disease Course Did Not Experience the Same Benefit as Those Treated Early



MEAD Study for Ozurdex



- Cataract
- 67.9, 64.1, 20.4 %

- IOP

All controlled with IOP

Surgery required in

2, 1, 0

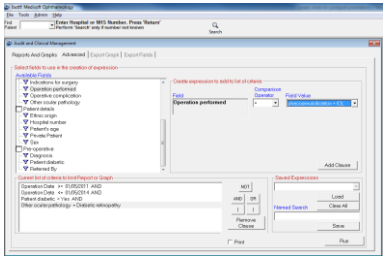
1. Identification of patients potentially suitable for 0.2 µg/day FAc implant[4]

- Diabetic patients
- HSE-confirmed grade M1 maculopathy
- Pseudophakic (i.e. cataract surgery performed)
- ≥3 consecutive intravitreal ranibizumab injections

Search period: May 2011 to December 2014

2. Assessment of insufficient response to ranibizumab treatment based on VA and CRT, according to baseline BCVA

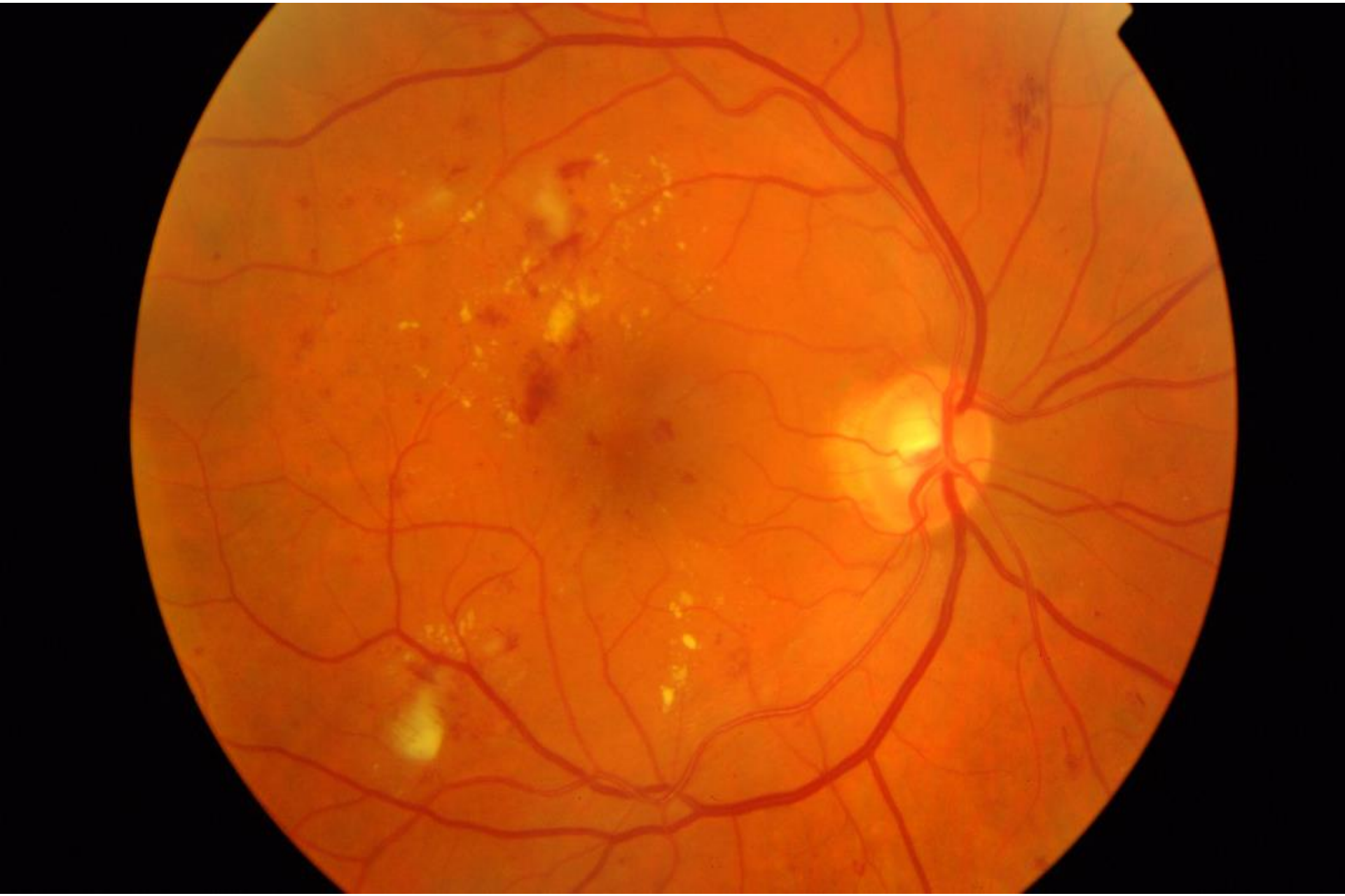
- BL BCVA <68 letters: CRT reduction ≤20% or no VA gain ≥5 letters
- BL BCVA ≥68 letters: CRT reduction ≤20% or VA loss >5 letters



3. If insufficiently responsive to prior ranibizumab treatment, patient records are flagged for the physician to consider 0.2 µg/day FAc implant

BCVA, best-corrected visual acuity; BL, baseline; CRT, central retinal thickness; FAc, fluocinolone acetonide; VA, visual acuity

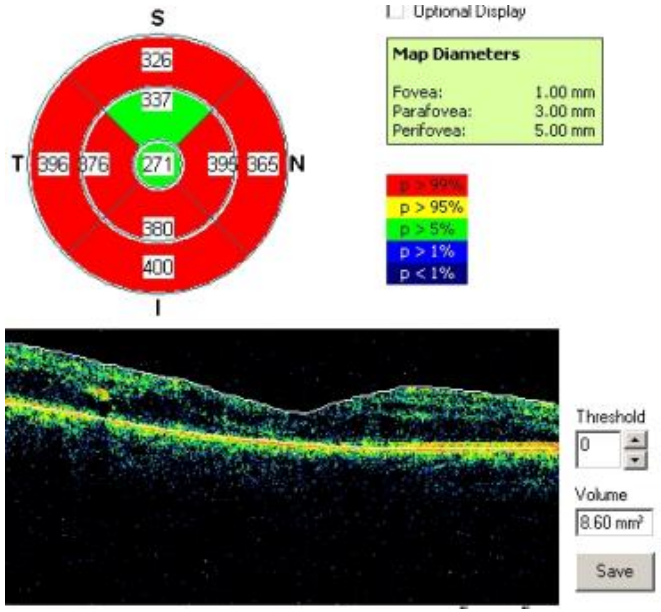
NICE TA 301.
http://www.nice.org.uk/guidance/ta301.
Published: November 2013



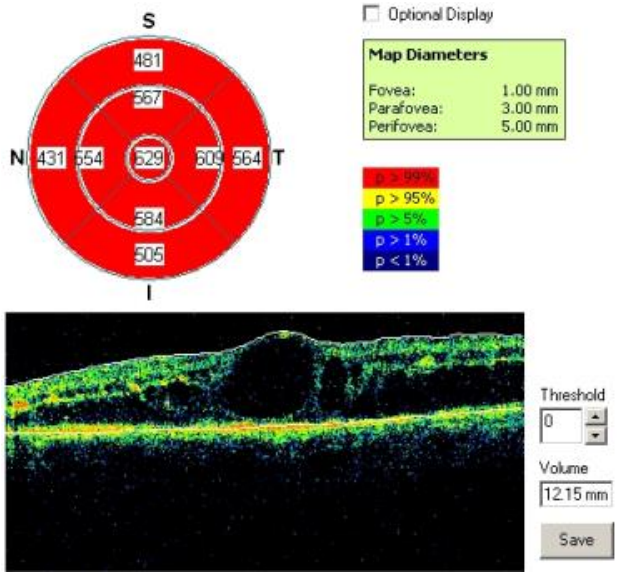
22/7/11 RE

DP, 62 Male, T2 DM : laser then IVI

- 6/2/13 VA 61

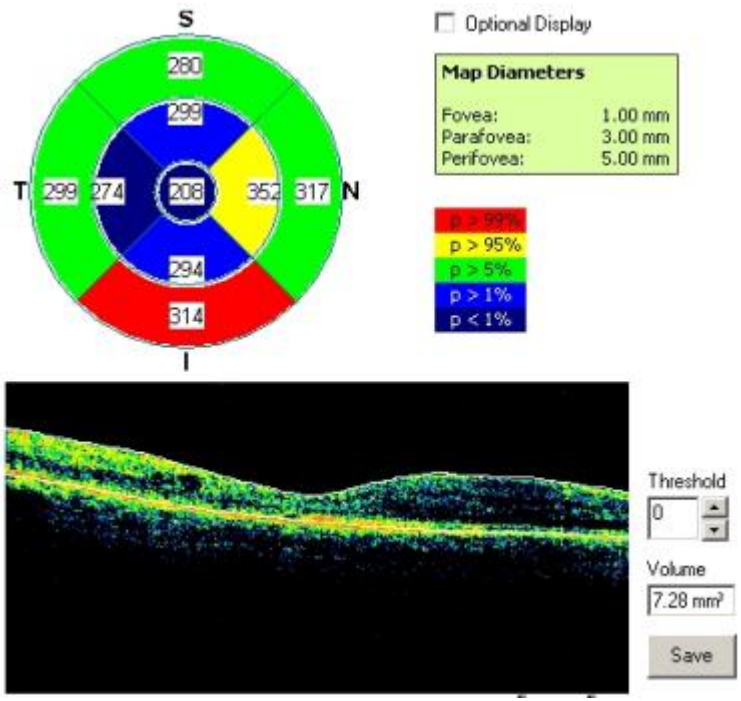


- VA 60

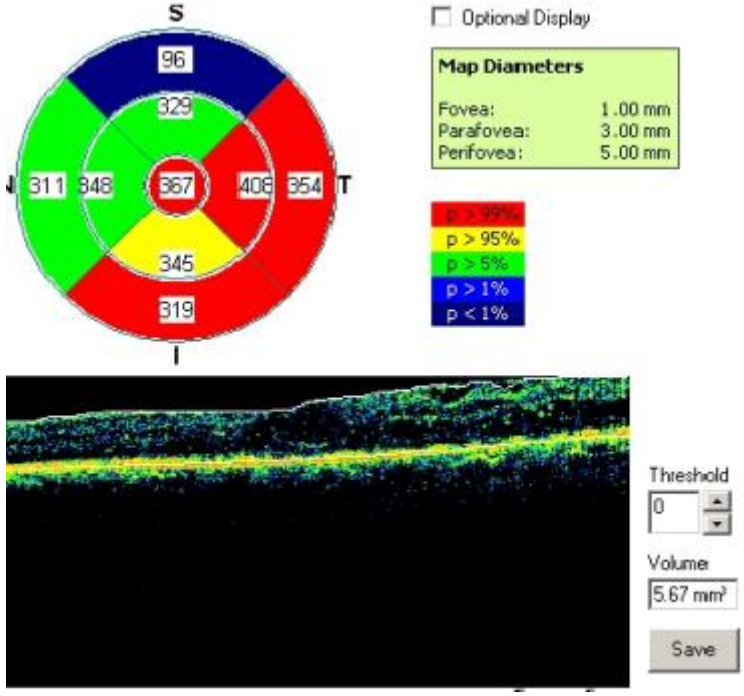


At 12/12 post Ranibuzumab PRN

- 20/1/14 VA 59 6 IVI

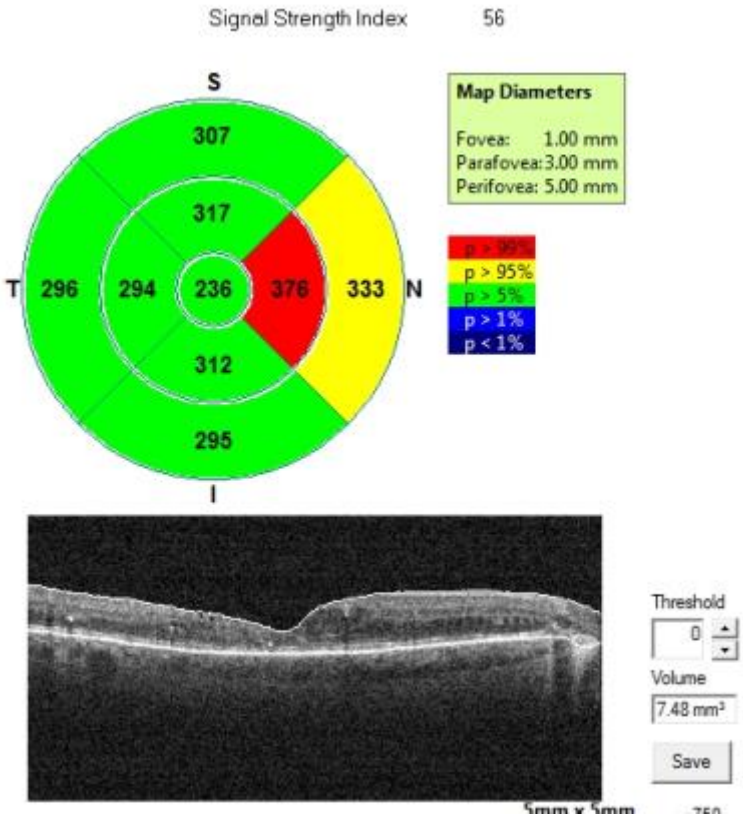


VA 52 8 IVI

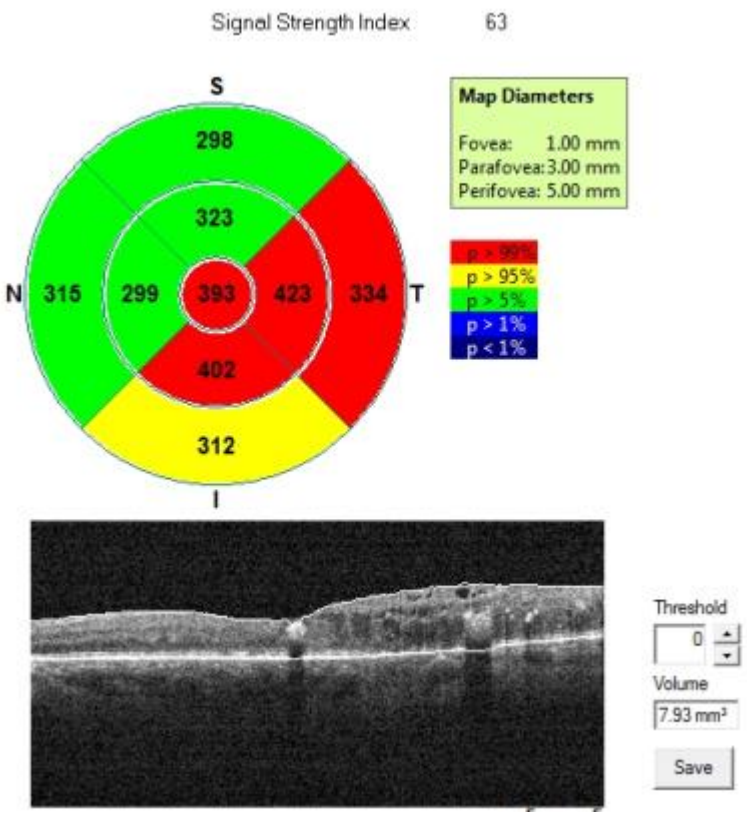


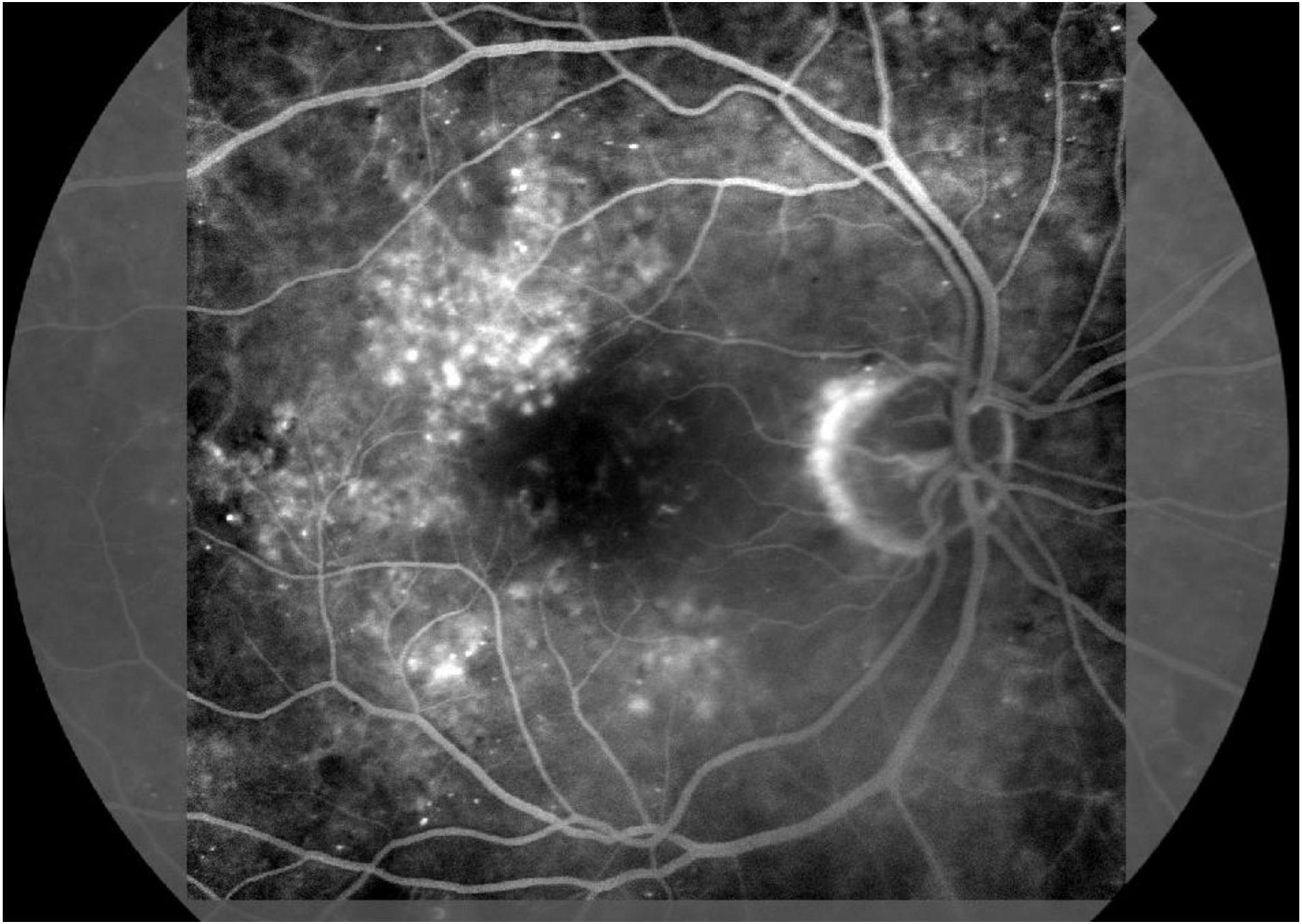
At 24 months post Ranibizumab

28/1/15 VA 70 0 IVI

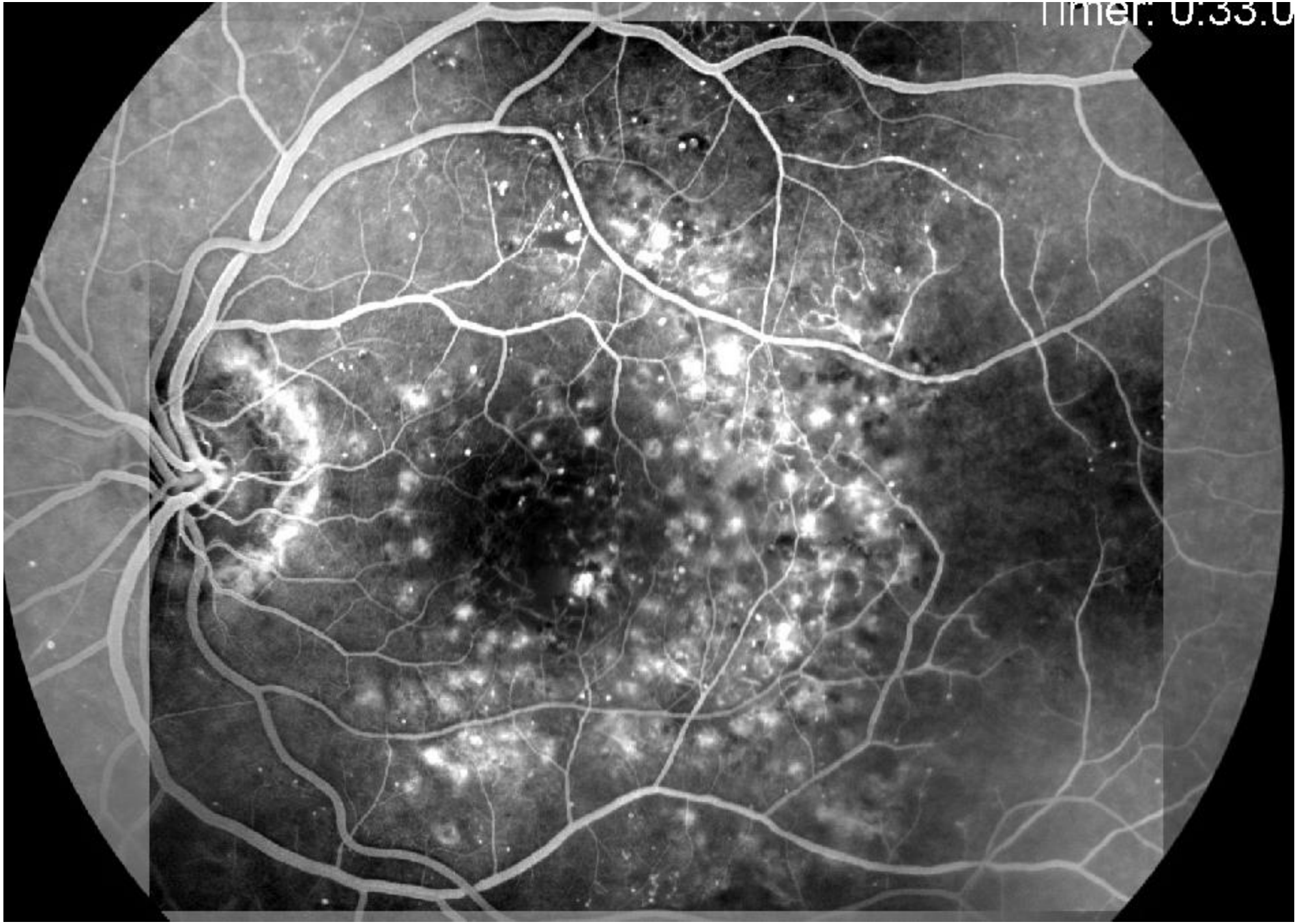


28/1/15 VA 55 3 IVI





21/9/15 VA 63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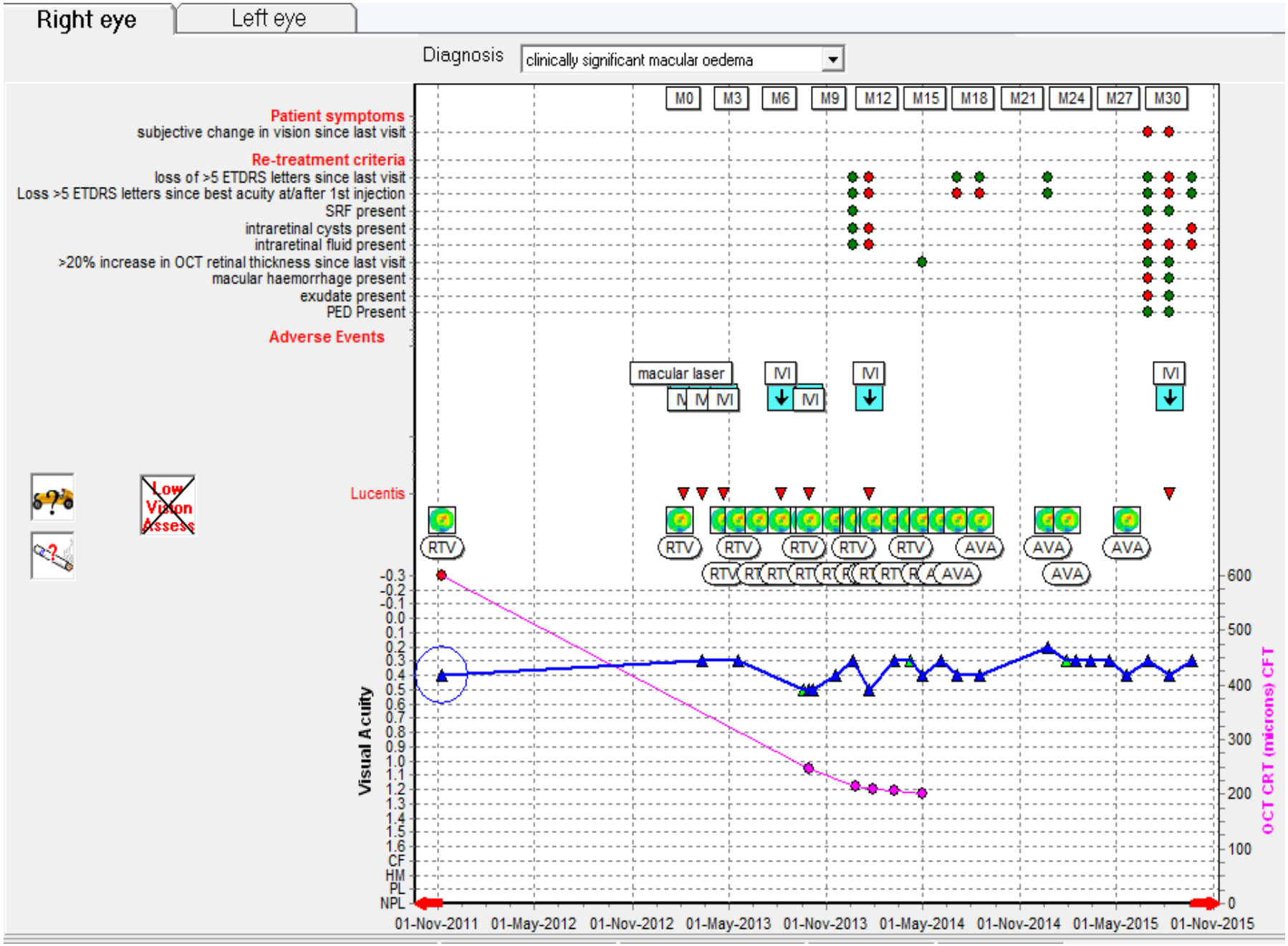
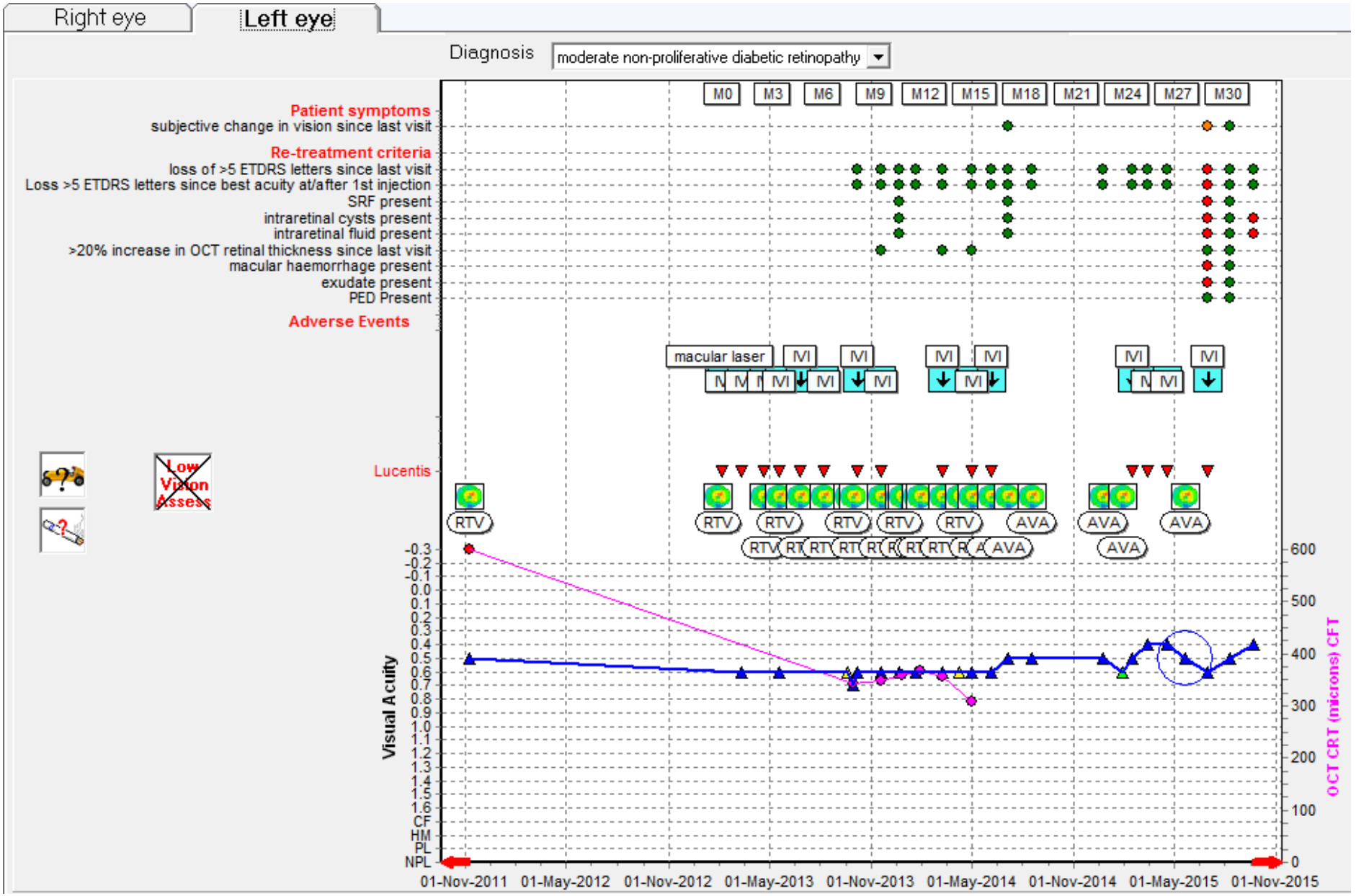

Right eye
Left eye
Diagnosis
clinically significant macular oedema
Patient symptoms
subjective change in vision since last visit
Re-treatment criteria
loss of >5 ETDRS letters since last visit
Loss >5 ETDRS letters since best acuity at/after 1st injection
SRF present
intraretinal cysts present
intraretinal fluid present
>20% increase in OCT retinal thickness since last visit
macular haemorrhage present
exudate present
PED Present
Adverse Events
Low Vision Assess
Lucentis
M0
M3
M6
M9
M12
M15
M18
M21
M24
M27
M30
macular laser
RTV
AVA
Visual Acuity
OCT CRT (microns) CFT
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
CF
HM
PL
NPL
600
500
400
300
200
100
0
01-Nov-2011
01-May-2012
01-Nov-2012
01-May-2013
01-Nov-2013
01-May-2014
01-Nov-2014
01-May-2015
01-Nov-2015


Right eye
Left eye
Diagnosis
moderate non-proliferative diabetic retinopathy
Patient symptoms
subjective change in vision since last visit
Re-treatment criteria
loss of >5 ETDRS letters since last visit
Loss >5 ETDRS letters since best acuity at/after 1st injection
SRF present
intraretinal cysts present
intraretinal fluid present
>20% increase in OCT retinal thickness since last visit
macular haemorrhage present
exudate present
PED Present
Adverse Events
Lucentis
Low Vision Assess
M0
M3
M6
M9
M12
M15
M18
M21
M24
M27
M30
macular laser
IVI
RTV
AVA
Visual Acuity
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
CF
HM
PL
NPL
OCT CRT (microns) CFT
600
500
400
300
200
100
0
01-Nov-2011
01-May-2012
01-Nov-2012
01-May-2013
01-Nov-2013
01-May-2014
01-Nov-2014
01-May-2015
01-Nov-2015

Challenges with care of DP

- Chronic DMO BE
- 2 laser 2011, 2013
- Again in 2015
- Combined with anti VEGF therapy (Ranibizumab)

Non visually significant cataracts (No history of glaucoma)
So ozurdex or Illuvien not an option in NHS

- Options
- Optimise systemic control
- Aflibercept?

- Future cataract progression
- Removal with caution as DMO present
- Consider steroid therpies

CRVO and MO in a Type 1 DM patient